

## **Anything goes?**

### **Regulation of the neural processes underlying response inhibition in TBI patients**

Short Title: Effects of methylphenidate on response inhibition after TBI

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## **Abstract**

Despite evidence for beneficial use of methylphenidate in response inhibition, no studies so far have investigated the effects of this drug in the neurobiology of inhibitory control in traumatic brain injury (TBI), even though impulsive behaviours are frequently reported in this patient group. We investigated the neural basis of response inhibition in a group of TBI patients using functional magnetic resonance imaging and a stop-signal paradigm. In a randomised double-blinded crossover study, the patients received either a single 30 mg dose of methylphenidate or placebo and performed the stop-signal task. Activation in the right inferior frontal gyrus (RIFG), an area associated with response inhibition, was significantly lower in patients compared to healthy controls. Poor response inhibition in this group was associated with greater connectivity between the RIFG and a set of regions considered to be part of the default mode network (DMN), a finding that suggests the interplay between DMN and frontal executive networks maybe compromised. A single dose of methylphenidate rendered activity and connectivity profiles of the patients RIFG near normal. The results of this study indicate that the neural circuitry involved in response inhibition in TBI patients may be partially restored with methylphenidate. Given the known mechanisms of action of methylphenidate, the effect we observed may be due to increased dopamine and noradrenaline levels.

**Keywords:** Traumatic Brain Injury, Response inhibition, Functional connectivity, Methylphenidate

## 1. Introduction

Although methylphenidate has an established beneficial effect over many of the cognitive functions typically impaired after traumatic brain injury (TBI) (Bales et al., 2009; Kim et al., 2006), the study of its effects on the neurobiological basis of response inhibition has not been assessed in this population even though impulsive behaviours and poor inhibitory control are frequently reported in patients with TBI. Such behavioural patterns not only have numerous repercussions on the patients' and relatives' quality of life but also have a negative impact on the rehabilitation process (Rochat et al., 2010). Moreover, despite the evidence for the beneficial use of methylphenidate in response inhibition paradigms in psychiatric and healthy populations (e.g., Aron et al., 2003; Rubia et al., 2014), no studies so far have investigated the effects of methylphenidate on the neurobiological basis of response inhibition in TBI patients.

In the context of response inhibition, the right inferior frontal gyrus (RIFG) has been postulated to be the main area associated with cognitive control (Aron et al., 2014). Nevertheless, high-level cognitive functions such as response inhibition require the integration of information across spatially distinct brain regions and therefore diffuse axonal injury (DAI) and its effect on long-range white matter tracts may be responsible for the compromised response inhibition found in TBI populations (Sharp et al., 2014). In this sense, the coordinated activity of large-scale brain networks such as the central executive, the salience and the default mode networks (DMN) seems to be necessary for efficient inhibitory control (Sharp et al., 2014). Studies of these networks in TBI populations have reported abnormally increased DMN connectivity as well as reduced connectivity between salience and DMN during the execution of response inhibition tasks (Hillary et al., 2011; Jilka et al., 2014; Pandit et al., 2013; Sharp et al., 2011; Tang et al., 2012; Venkatesan et al., 2015). Interestingly, the failure to regulate the activity/connectivity of the DMN or the lack of

deactivation of this network during the execution of inhibition tasks has been associated with slower and less successful inhibitory control (Bonnelle et al., 2012; Raichle and Snyder, 2007; Zhang and Li, 2012)

In this study we investigated the neural basis of response inhibition in a sample of TBI patients and an age-matched control group using functional magnetic resonance imaging and a stop-signal paradigm. In a randomised double-blinded crossover study, the patients received either a single 30 mg dose of methylphenidate or placebo and performed the stop-signal task. Healthy controls (HC) underwent the same protocol without methylphenidate. We hypothesize that chronic TBI patients will show reduced activity in the areas associated with inhibitory control (e.g., inferior frontal gyrus) and that the use of a single dose of methylphenidate will restore the functionality of these regions by increasing dopamine and noradrenaline levels (Chamberlain et al., 2007, 2009).

## **2. Experimental procedures**

### **2.1. Participants**

Fourteen chronic TBI patients and 20 HC met the study inclusion criteria. TBI patients were referred from the Addenbrooke's Neurosciences Critical Care Unit Follow-Up Clinic, the Addenbrooke's Traumatic Brain Injury Clinic and the Royal London Hospital Intensive Care Unit. Only patients with DAI, as opposed to focal lesions, were included in this study. They were at least 7 months post TBI (mean  $20.79 \pm 11.78$  months) and were not receiving any acute hospital interventions. They sustained moderate to severe TBI –as measured by the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974), the Injury Severity Scale (ISS) (Baker et al., 1974) and the Acute Physiology and Chronic Health Evaluation II (APACHE II) (Knaus et al., 1985). Lesion information of the patients is presented in Supplementary Table 1. HCs were recruited via advertisements in Addenbrooke's Hospital and in the local

Cambridge area and were paid for their participation. Both HCs and TBI patients were screened by exclusion criteria including National Adult Reading Test < 70, Mini Mental State Exam < 23, left-handedness, history of psychiatric or neurologic disorders, contraindications for MRI scanning, taking medication that may affect their physical or cognitive performance, history of drug or alcohol abuse and pregnancy or nursing. Additionally, patients were excluded if they had a physical disability that could prevent them from completing the tasks either in the screening or scanning stages. Demographic and characteristics of the samples are summarized in Table 1.

## 2.2. Testing protocols and procedures

This study was approved by the local Research Ethics Committee and exempted from Clinical Trials status by the United Kingdom's Medicines and Healthcare products Regulatory Authority. All participants provided written informed consent and healthy controls received monetary compensation for their participation. The testing protocol included two visits separated by 2-4 weeks. During the first visit and prior to receiving any medication, a series of background assessments and a baseline cognitive assessment (lasting approximately 60 minutes) were carried out in both groups, outside the scanner. We used a cognitive battery designed to measure several aspects of executive function plus reaction time through well-validated tests. MRI scanning was carried out during both visits and lasted approximately 90 minutes. The effects of methylphenidate on the neural substrates of response inhibition were assessed in a within-subject, double-blind, crossover, randomized, placebo-controlled design, with participants visiting on two occasions. On one of the two visits (randomized order) the TBI patients ingested a single capsule containing 30 mg of methylphenidate and during the other, a placebo capsule of identical appearance containing lactose. The 30-mg dose of methylphenidate was chosen to match the doses used in clinical practice and reported in the literature (e.g., Gilbert et al, 2006; Marquand et al., 2011).

Patients relaxed for 1.5 hours in a quiet waiting room, before undertaking brain scanning to ensure peak plasma levels were reached (Faraj et al., 1974). HC attended their two fMRI assessments at the same time interval as for the drug/placebo patient arm of the study, but without pharmacological intervention.

## 2.3. Instruments

### 2.3.1. Executive function tests

We used a cognitive battery designed to measure several aspect of executive function plus attention through well-validated tests. The measures of executive function we used were the spatial span test (SSP) and the intra-extra dimensional set shift (IED). Both measures along with the measure of simple reaction time (SRT) are part of the Cambridge Neuropsychological Test Automated Battery (CANTAB; <http://www.cambridgecognition.com/>). The validity of the CANTAB has been supported by numerous studies in patients with brain lesions, neurodegenerative diseases, and psychiatric illness (e.g., Chamberlain et al., 2011; Kasahara et al., 2011). The SSP assesses working memory capacity. A set of white squares is shown on the screen. Some of the squares change in colour, one by one, in a variable sequence. At the end of each sequence a tone indicates that the subject should touch each of the boxes coloured by the computer in the same order as they were originally presented. The number of squares ranges from two to nine. The analysis of the SSP focuses on the spatial span length and total errors. The IED test assesses visual discrimination and attentional set formation and maintenance, shifting, and attentional flexibility. The test initially presents two simple coloured shapes and the participant must determine which one is correct in response to feedback. In successive stages when a criterion is reached (i.e., six correct responses), the rules and/or stimuli change, moving from intra-dimensional, in which coloured shapes remain the only relevant dimension, to extra-

dimensional, in which the participant needs to shift between white lines and coloured shapes as relevant or irrelevant dimensions. Finally, the simple reaction time (SRT) is a test which assesses reaction time. It is useful for testing general alertness and motor speed. The participant must press a button as soon as he/she sees a white square on the screen.

### 2.3.2. Stop-Signal Task

The stop-signal event-related fMRI paradigm has been described and validated in detail elsewhere (Rubia et al., 2003; 2007). All participants received a training session outside the scanner to ensure correct understanding of the task instructions. On each trial, a left- or right-pointing arrow is displayed on a computer screen (white on black background) and volunteers are instructed to respond with their right index or middle fingers depending on the arrow direction (go trials). In some trials, the arrow is followed by another arrow pointing upwards (stop trials) in which case the participants are instructed to stop themselves from pressing any buttons. Nevertheless, motor responses are made prepotent by the infrequent nature of stop trials. The interval between the onset of the go trial and the onset of the stop trials (i.e., stop-signal delay -SSD) was set at 150 ms on the first stop trial. From then on, an online tracking algorithm adjusted SSD as a function of individual stopping performance (Levitt, 1971). After successful inhibition, SSD increased by 50 ms, thereby decreasing the chances of successful inhibition on the next stop trial. If the participant was unable to stop (i.e., failed-inhibition trial), SSD decreased by 50 ms, increasing the chances of stopping. This adaptive algorithm ensured successful inhibition on about 50% of the stop trials, a procedure that yields reliable estimates of SSRT (Band et al., 2003). The task included 240 trials in total, 200 go trials and 40 stop trials. The minimum number of go trials between two stop trials was three and the maximum seven. The go stimulus duration in go trials was 1000 ms, whereas the stop stimulus duration varied between a minimum of 100 ms and 300 ms. Inhibitory control was evaluated using the stop-signal reaction time (SSRT). SSRT was

calculated by subtracting mean SSD from the median reaction time on go trials. SSRT thus reflects the average time (in ms) that the individual requires in order to successfully inhibit a motor response approximately 50% of the time and therefore higher SSRT values are indicative of poorer inhibition (Logan et al., 1997).

## 2.4. MRI acquisition and pre-processing

Participants were scanned on a Siemens Trio 3-Tesla MR system (Siemens AG, Munich, Germany) at the Wolfson Brain Imaging Centre of Addenbrooke's Hospital (Cambridge, UK). The imaging session started with a localiser followed by a high resolution T1-weighted, magnetization-prepared 180 degrees radio-frequency pulses, rapid gradient-echo (MPRAGE) structural scan (TR = 2300 ms, TE = 2.98 ms, TA = 9.14 min, flip angle = 9°, FOV = 256 mm, voxel size = 1.0 x 1.0 x 1.0 mm, slices = 176). DTI data (63 non-collinear directions, b = 1000 s/mm<sup>2</sup> with one volume acquired without diffusion weighting (b = 0), TR = 1700 ms, TE = 106 ms, FOV = 192 mm, voxel size = 2.0 x 2.0 x 2.0 mm) were also collected to investigate white matter integrity in the TBI group. Finally, the functional data was acquired using an EPI (echo-planar imaging) sequence with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 78°, FOV = 192 mm, voxel size = 3.0 x 3.0 x 3.75 mm, slices per volume = 32.

DTI data were eddy current corrected and realigned using FSL ([fsl.fmrib.ox.ac.uk/fsl/fslwiki/](http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/)). Fractional anisotropy images were calculated and spatially normalised by utilising a study specific template constructed in a manner described by our group previously (Stamatakis et al., 2011). The spatially normalised fractional anisotropy images were smoothed with an 8 mm isotropic Gaussian filter. Functional MRI data were preprocessed using SPM8 (Wellcome Department of Cognitive Neurology, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) implemented in MatLab R2007b



(Mathworks, Natick, MA, USA). fMRI image preprocessing involved motion correction, spatial normalization to the MNI space and smoothing with a 6 mm FWHM Gaussian kernel.

## 2.5. Behavioural analyses

Behavioral data were analysed with the SPSS 21 (Chicago, IL, USA). Independent-sample *t*-test and chi-square tests were used to compare the groups on relevant socio-demographic variables. Finally, a Kruskal-Wallis test was used to test for differences between groups (HC and TBI patients under the placebo and Methylphenidate condition) on the SSRT since the scores of the participants were not normally distributed. Because inhibitory control may be influenced by other cognitive processes, we also performed bivariate correlations between the measure of inhibition we used (SSRT) and simple reaction time (SRT), working memory (SSP) and cognitive flexibility (IED) measures, assessed in the group of TBI patients during their first visit before the administration of either drug or placebo. Significance threshold was set at  $P < 0.05$ .

## 2.6. Imaging analyses

### 2.6.1. DTI Analysis

Voxel-wise group fractional anisotropy comparisons between HC and TBI patients were carried out using a two-sample *t*-test. The data of one patient and three HCs did not meet our quality assessment criteria and were not included in these analyses. Clusters are reported as significant if they survived FWE correction for multiple comparisons set at  $P < 0.05$  (individual voxel threshold was set at  $P < 0.001$  uncorrected). Significant clusters were anatomically annotated using the natbrainlab.nii.gz template (<http://www.mccauslandcenter.sc.edu/mricro/mricron/>).

### 2.6.2. fMRI Analysis

The BOLD response at each voxel was convolved with the canonical hemodynamic response function and a high-pass filter was used to remove low-frequency noise (1/120 Hz). The conditions of interest were modelled from the onset of the go and no go trials and six additional regressors were included in the model accounted for subject movement. We defined four conditions of interest based in the participants' response: go success, go error, stop success and stop error. We were interested in studying brain activation for the contrast of stop success and stop error. We were interested in studying brain activation for the contrast of stop success vs. stop error which served as a measure of inhibitory control. Within group activation maps were obtained with one-sample t-tests. Differences between the groups were established using two-sample t-tests. We report group differences using small volume correction. To avoid circularity we defined a region of interest (ROI) derived from a different group of subjects (from the study of Rubia et al., 2003) and included significantly activated areas for the contrast of successful inhibition vs. unsuccessful inhibition (or stop success > stop error). Statistical significance was established with a combination of voxel- and cluster-level thresholds. The spatial extent thresholds were determined by 1000 Monte Carlo simulations using AlphaSim (Ward, 2000) as implemented in the SPM REST toolbox (Song et al., 2011). Input parameters to AlphaSim included a probability voxel-level significance of 0.005, a cluster connection radius of 5 mm and the smoothness of each T map within our ROIs after model estimation. The minimum cluster size to satisfy a  $P < 0.05$  FWE were 207 voxels for the one-sample t-test and 26 for the two-sample t-test.

### 2.6.3. Psychophysiological interactions analysis

To examine changes in effective connectivity between groups during the experimental task, we conducted a Psychophysiological interaction (PPI) analysis which involves the extraction of a task specific time-series from an ROI (seed) and the calculation of its interactions with

other parts of the brain in a voxel-wise manner. The seed region selected in this instance was defined as a 6 mm radius sphere around the significant statistical peaks found from the group activity comparison. In this analysis and due to the lack of an a priori hypothesis, input parameters to AlphaSim were the same as those we used in the subtractive fMRI analysis but including a gray-matter whole brain mask of 163,556 voxels and the actual smoothing of the data after model estimation. The minimum cluster size was determined to be 180 voxels for the one sample t-test and 174 voxels for the two sample t-test to satisfy a family-wise error rate correction of  $P < 0.05$  FWE.

#### 2.6.4. Functional connectivity/behaviour relationships

The RIFG connectivity maps for each participant (as described above) were entered into a voxel-wise linear regression analysis to assess between-group differences in the correlation between the score of SSRT and functional connectivity. In this set of analysis and due to the lack of a previous hypothesis, input parameters to AlphaSim were the same as those we used in the subtractive fMRI analysis but including a gray-matter whole brain mask of 163,556 voxels and the actual smoothing of the data after model estimation. The minimum cluster size was determined to be 180 voxels for the one sample t-test and 174 voxels for the two sample t-test to satisfy a family-wise error rate correction of  $P < 0.05$  FWE.

### 3. Results

#### 3.1. Behavioral analysis

Both groups had statistically equivalent distributions for age (HC  $34.15 \pm 11.12$  vs. TBI patients  $36.86 \pm 14.17$ ;  $P = 0.537$ ) and verbal IQ (HC  $117.05 \pm 5.87$  vs. TBI patients  $111.93 \pm 10.69$ ;  $P = 0.120$ ) and were matched on gender (HC 60% vs. TBI patients 71.4% male;  $P = 0.493$ ) (Table 1). Successful inhibition to stop trials was close to 50% in all subjects, thus

proving that the tracking stop mechanism which aimed to ascertain that each subject was working at the edge of his/her own inhibitory capacity was successful. Univariate ANCOVAs showed no group differences in performance. Nevertheless, the scores of the measure of impulsivity showed that TBI patients were more impulsive than HC and that the use of a single dose of methylphenidate had a positive effect over inhibition (HC  $158.82 \pm 115.05$  vs. TBI placebo  $189.14 \pm 123.54$  vs. TBI drug  $174.66 \pm 110$ ;  $P = 0.750$ ). When the relationship between SSRT and attention and executive functioning were assessed, we found no significant correlations between any of these measures: SRT (placebo  $r = 0.294$ ,  $p = 0.308$ ; drug  $r = -0.046$ ,  $p = 0.875$ ), SSP (placebo  $r = -0.323$ ,  $p = 0.260$ ; drug  $r = -0.504$ ,  $p = 0.066$ ), IED (placebo  $r = -0.010$ ,  $p = 0.973$ ; drug  $r = -0.411$ ,  $p = 0.144$ ).

### 3.2. Imaging analyses

#### 3.2.1. DTI analysis

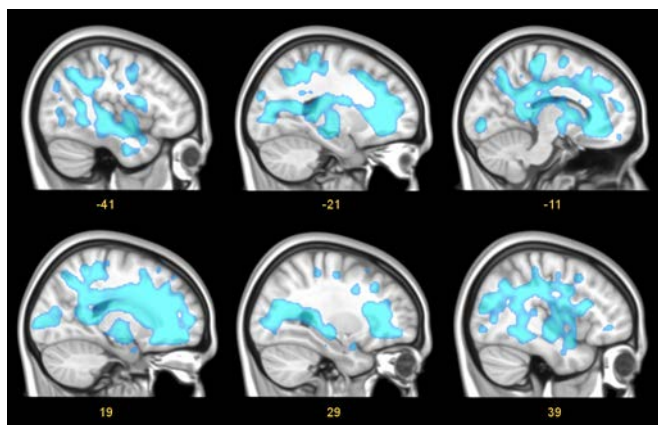
As expected from a group of patients with DAI, we observed wide-spread reductions in fractional anisotropy in the TBI patients when compared to the HC group (Figure 1). Statistical peaks for differences were detected in the left inferior parietal cortex ( $x, y, z = -55, -26, 41$ ;  $t_{28} = 7.35$ ) and the left posterior ( $x, y, z = -48, -50, 32$ ;  $t_{28} = 7.59$ ) and right anterior aspect of the arcuate ( $x, y, z = 33, 6, 35$ ;  $t_{28} = 7.33$ ) signifying wide-spread fronto-parietal disconnections.

#### 3.2.2. Subtractive fMRI analysis

Intra-groups activations. Activation maps for the groups are shown in Figure 2. HC significantly activated a region encompassing the RIFG extending to the anterior insula (peak at  $x, y, z = 32, 20, -6$ ;  $t_{19} = 5.29$ ) and the superior parietal cortex (peak at  $x, y, z = 24, -64, 52$ ;  $t_{19} = 8.13$ ). Additionally, this group showed significant deactivations in the postcentral gyrus

(peak at  $x, y, z = -36, -22, 48$ ;  $t_{19} = 7.07$ ) and rolandic operculum (peak at  $x, y, z = -40, -22, 16$ ;  $t_{19} = 4.86$ ). We did not find any significant activations or deactivations in the two TBI conditions (placebo or drug) at  $P < 0.05$  FWE; we are however showing TBI group activations and deactivations at  $P < 0.005$ ,  $k > 50$  for exploratory purposes only (Figure S1).

Group differences. When compared with HC, only TBI patients on placebo showed significantly reduced activation in the RIFG (peak at  $x, y, z = 40, 32, -6$ ;  $t_{32} = 3.43$ ), indicating activity normalization of this region during the methylphenidate condition. We used the statistical peak from the RIFG as a seed to explore connectivity differences between the groups (HC vs. TBI).

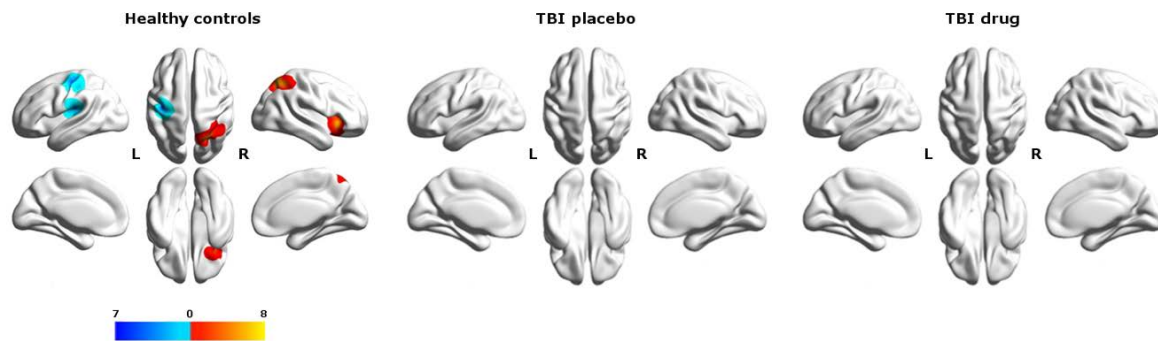


**Figure 1.** Pattern of fractional anisotropy reductions found in the chronic TBI patients compared to the control group. Results are shown on an MNI template and the numbers correspond to the  $x$  coordinates.

### 3.2.3. Psychophysiological interactions analysis

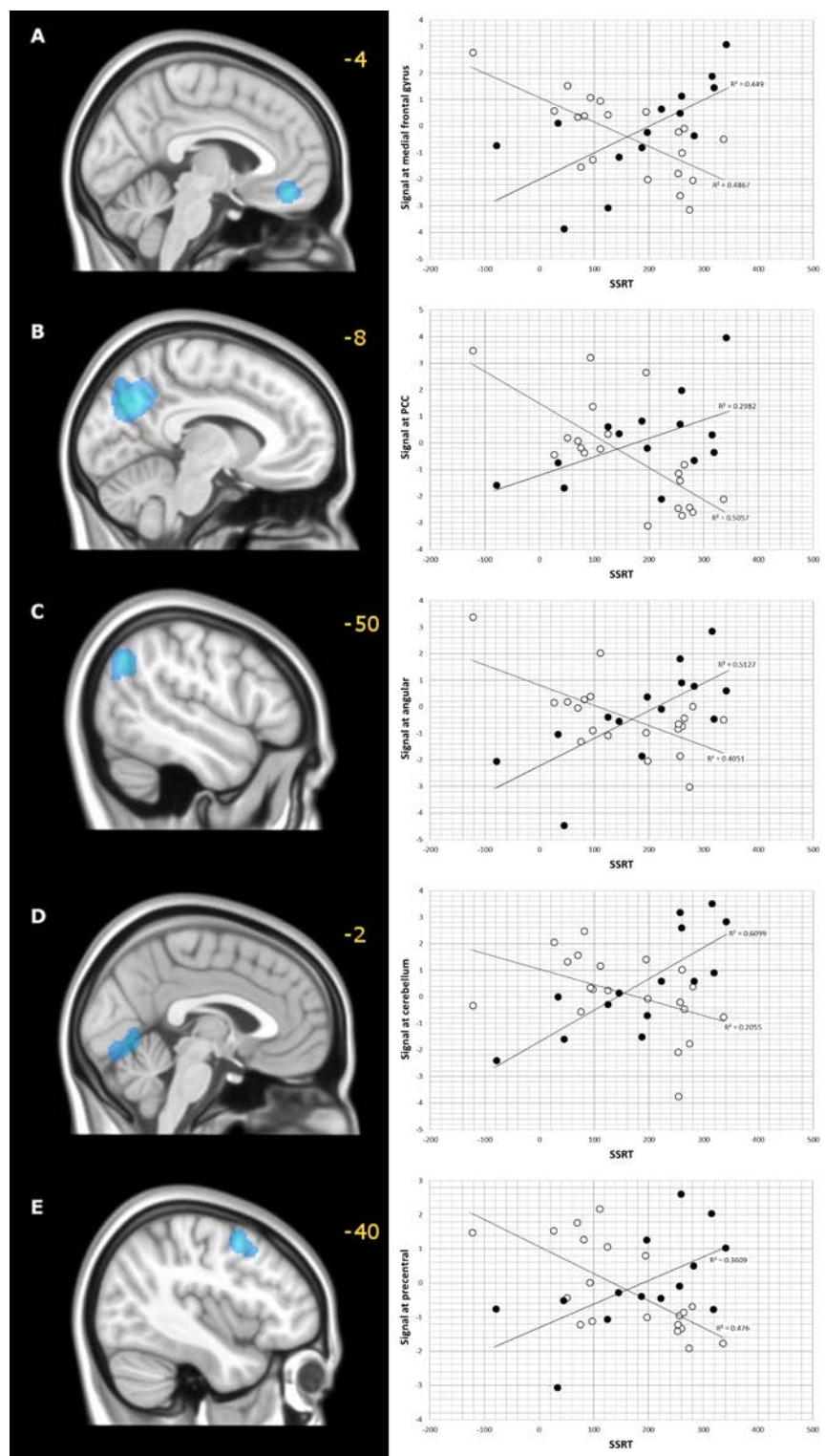
Intra-groups connectivity maps. Connectivity maps for the groups are shown in Figure S2. HC showed negative connectivity between the RIFG and the left anterior cingulate cortex (peak at  $x, y, z = -2, 40, 16$ ;  $t_{19} = 4.83$ ), postcentral gyrus (peak at  $x, y, z = -42, -30, 52$ ;  $t_{19} = 5.29$ ), putamen (peak at  $x, y, z = -24, 12, -6$ ;  $t_{19} = 4.14$ ), cerebellum (peak at  $x, y, z = -42, -58, -34$ ;  $t_{19} = 5.42$ ) and the right inferior parietal (peak at  $x, y, z = 38, -40, 54$ ;  $t_{19} = 4.56$ ) and

occipital cortices (peak at  $x, y, z = 42, -82, -10$ ;  $t_{19} = 4.20$ ). TBI patients in the placebo condition showed positive correlations with the left putamen (peak at  $x, y, z = -32, -10, -4$ ;  $t_{13} = 5.66$ ) and right cerebellum (peak at  $x, y, z = 14, -32, -24$ ;  $t_{19} = 5.59$ ). Finally, TBI patients in the drug condition showed negative correlations with the right inferior temporal cortex (peak at  $x, y, z = 54, -68, -12$ ;  $t_{13} = 6.47$ ).



**Figure 2.** Brain activations and deactivations found during the successful inhibition vs. unsuccessful inhibition contrast in the groups. HC significantly activated a region encompassing the RIFG extended to the anterior insula and the superior parietal cortex. Additionally, this group showed significant deactivations in the postcentral gyrus and rolandic operculum. We did not find any significant activations or deactivations in the groups of TBI patients. Results are presented on inflated brains created using the BrainNet tool. The colour bars represent t-values.

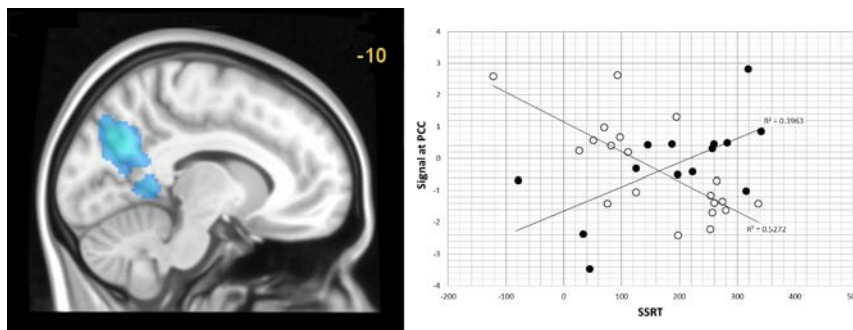
Group differences. Between-group comparisons revealed that when compared with HC, TBI patients on placebo presented increased functional connectivity between the RIFG and two regions encompassing the putamen and amygdala bilaterally. Notably, there were no significant connectivity differences between HC and TBI patients after the administration of a single dose of methylphenidate, which may suggest drug modulation of RIFG connectivity.



**Figure 3.** Clusters and plots of the interactions found between SSRT scores and the connectivity between the inferior frontal gyrus *seed*. **(A)** Clusters and plots of the interactions found between SSRT scores and the connectivity between the inferior frontal gyrus and the medial frontal gyrus, **(B)** Clusters and plots of the interactions found between SSRT scores and the connectivity between the inferior frontal gyrus and the PCC, **(C)** Clusters and plots of the interactions found between SSRT scores and the connectivity between the inferior frontal gyrus and the angular gyrus, **(D)** Clusters and plots of the interactions found between SSRT scores and the connectivity between the inferior frontal gyrus and the cerebellar vermis, **(E)** Clusters and plots of the interactions found between SSRT scores and the connectivity between the inferior frontal gyrus and the precentral gyrus. TBI patients in the placebo condition (filled circles, solid line) showed significant positive correlations, while the HC (open circles, dotted line) displayed a negative correlation with SSRT.

### 3.2.4. Connectivity/behaviour relationships

A significant between-group interaction was found between the SSRT scores and the connectivity between the RIFG and a set of regions in the medial surface of the cortex known as the DMN (Buckner et al., 2008; Greicius et al., 2003; Raichle et al., 2001). Specifically, greater SSRT scores were associated with higher connectivity between RIFG and the left medial frontal gyrus (peak at  $x, y, z = -4, 42, -18$ ;  $t_{30} = 5.13$ ), the posterior cingulate cortex (PCC) (peak at  $x, y, z = -8, -74, 34$ ;  $t_{30} = 4.64$ ), the angular gyrus (peak at  $x, y, z = -50, -68, 40$ ;  $t_{30} = 5.06$ ), the cerebellar vermis (peak at  $x, y, z = -2, -68, -6$ ;  $t_{30} = 4.45$ ) and the precentral gyrus (peak at  $x, y, z = -40, 4, 48$ ;  $t_{30} = 4.67$ ) in the TBI group in the placebo condition and lower connectivity in the HC group (Figure 3). The administration of methylphenidate in the patients attenuated all the above interactions with the exception of the PCC. Specifically, when patients took methylphenidate we found a significant between-group interaction between the SSRT scores and the connectivity between the RIFG and the PCC (peak at  $x, y, z = -10, -66, 30$ ;  $t_{30} = 5.40$ ). In other words, greater SSRT scores were associated with higher connectivity in the TBI group in the drug condition and lower connectivity in the group of HC (Figure 4).



**Figure 4.** Clusters and plots of the interactions found between SSRT scores and the connectivity between the inferior frontal gyrus *seed* and the posterior cingulate cortex. TBI patients in the drug condition (filled circles, solid line) showed significant positive correlations, while in HC (open circles, dotted line) the correlations were negative.



#### **4. Discussion**

The current study aimed to investigate the effect of the administration of a single dose of methylphenidate in TBI survivors during the execution of a response inhibition task. We found activity abnormalities in the patients as well as compromised functional connectivity which we related to performance. The patients also presented with reduced fractional anisotropy across most white matter tracts. Both activity and connectivity normalised after the administration of methylphenidate. It is important to note that this study included only patients in the chronic phase of brain injury and therefore, the alterations we found not only highlight the chronic nature of this disorder but also the fact that chronic TBI patients may benefit from the use of methylphenidate.

In keeping with previous work, we found significant reduced fractional anisotropy in the patient group providing evidence for the presence of traumatic axonal injury (e.g., Kinnunen et al, 2011; Sharp et al, 2011). We also found, in line with previous imaging studies on the stop-signal task, that inhibitory control was mediated by the RIFG (e.g., Aron et al., 2014; Rubia et al., 2003; Sharp et al., 2010). Furthermore, the improved inhibitory response together with the increased activation of this region after the administration of a single dose of methylphenidate is consistent with studies showing the benefits of this drug on response inhibition in both HC and patients (e.g., ADHD) (Aron et al., 2003; Costa et al., 2013; Pauls et al., 2012; Rubia et al., 2014).

The increased functional connectivity we found in the TBI patient group between the RIFG and the amygdala and the dorsal striatum overlaps with studies showing enhanced connectivity during recovery in this population. Specifically, it has been shown that several neural networks present increased connectivity during the first year of recovery after TBI, and that this change is disproportionately represented in brain regions belonging to the brain's

core networks (i.e., salience, central executive and DMN) (Hillary et al., 2011, 2014). The detected increased connectivity may provide evidence for the existence of a mechanism compensating for alterations in the networks associated with response inhibition. Along the same lines, activity in the basal ganglia has been shown to correlate with SSRT and to be more strongly activated in volunteers who perform better in this task (Vink et al., 2005). There is also evidence for a direct link between dopamine-receptor availability in the striatum and response inhibition (Ghahremani et al., 2012).

The interaction found between the SSRT scores and the connectivity between the RIFG and several regions of the DMN (e.g., medial frontal gyrus, PCC, angular and cerebellar vermis) indicates that in TBI patients on placebo, greater connectivity with the DMN is associated with longer SSRT or poorer inhibitory control, in agreement with studies showing that efficient stopping is associated with the deactivation of the DMN (Bonnelle et al., 2012; Raichle and Snyder, 2007; Zhang and Li, 2012). DMN activity is normally high when attention is internally directed, and during actions that are reasonably automatic and low when responding to an unexpected event in the environment such a stop signal (Andrews-Hanna et al., 2010; Fox and Raichle, 2007; Raichle et al., 2001). When responding to an unexpected event, this internally focused mode of operation needs to be inhibited, allowing the brain to rapidly switch to a controlled mode whereby actions are tightly coupled to external events. Therefore, the correlations we found may indicate damage in the networks involved in the regulation of the DMN (i.e., salience and central executive networks), which might produce ‘interference’ to normal network operations (Bonnelle et al., 2012; Chen et al., 2013; Gao and Lin, 2012; Jilka et al., 2014; Sharp et al., 2014; Wen et al., 2013). A pattern that has also been found in other disorders characterized by lack of inhibitory control (Fassbender et al., 2009; van Rooij et al., 2015).

Interestingly, the complex relationship we found between the RIFG and the majority of the DMN areas in the placebo condition disappears in the drug condition, indicating that the administration of methylphenidate may promote a normal balance between the DMN and inhibition networks. In this sense, the use of a single dose of methylphenidate has been associated with the reduction or “normalization” of abnormally high resting state functional connectivity seen in people with ADHD (An et al., 2013; Silk et al., 2016), a population with similar inhibitory control problems. Moreover, and in concordance with our findings, a number of task-based functional connectivity studies have demonstrated that a single dose of methylphenidate improves the suppression of the default mode network (Liddle et al., 2011; Peterson et al., 2009; Sripada et al., 2013; Tomasi et al., 2011). It is worth noting that the use of methylphenidate did not affect the association between SSRT scores and connectivity between the RIFG and the PCC. The PCC has dense connections to many cortical regions, and it is considered to be part of the brain’s structural core (Buckner et al., 2008; Greicius et al., 2009; Hagmann et al., 2008). It has also been described as a major DMN node which together with its implication in a number of neuropsychiatric and neurodegenerative diseases suggests that this region has a central role in cognition (Leech and Sharp, 2014). Moreover, the fact that several TBI studies have reported the functional alteration of this area, specifically during the execution of inhibition tasks, indicates that this structure may play an important role in response inhibition (Bonnelle et al., 2012; Pandit et al., 2013; Sharp et al., 2011).

Together, these data suggest that the dysfunctional systems underlying response inhibition deficits in TBI patients may be partially restored by methylphenidate which has been shown to increase dopamine and noradrenaline neurotransmission by blocking their re-uptake. Nevertheless and since there is not much of a difference between the group SSRT scores when the error is considered, futures studies with bigger sample size should explore

the possible existence of subgroups within the study groups (i.e., subgroups with good/bad outcomes as well as drug responders). Moreover, it is worth mentioning that we did not find any association between SSRT and measures of attention or executive function we used and therefore we propose that our results cannot be explained by deficits in these cognitive domains. However, in order to know the exact mechanism of action of methylphenidate, future studies should assess other cognitive variables that could further elucidate findings such as ours. Likewise, future studies and clinical trials should assess the long-term effect of methylphenidate in the treatment of impulsivity and other cognitive disorders following TBI. One of the strengths of our study is the inclusion of a HC group matched in the main socio-demographic variables and the utilization of a well-validated measure of response inhibition. Nevertheless, several limitations are worth noting. First, although comparable with previous studies, it would be important to replicate this study with a larger sample size. Second, it should be noted that the methods used to assess functional connectivity cannot determine the direction of connectivity. In the future, techniques such as dynamic causal modelling could be used. Finally, this study would have benefited from the inclusion and analysis of the sleep parameters of the groups given that sleep is a major complaint in chronic TBI sufferers and it has been associated with response inhibition deficits (Gardani et al., 2015; Sagaspe et al., 2007).

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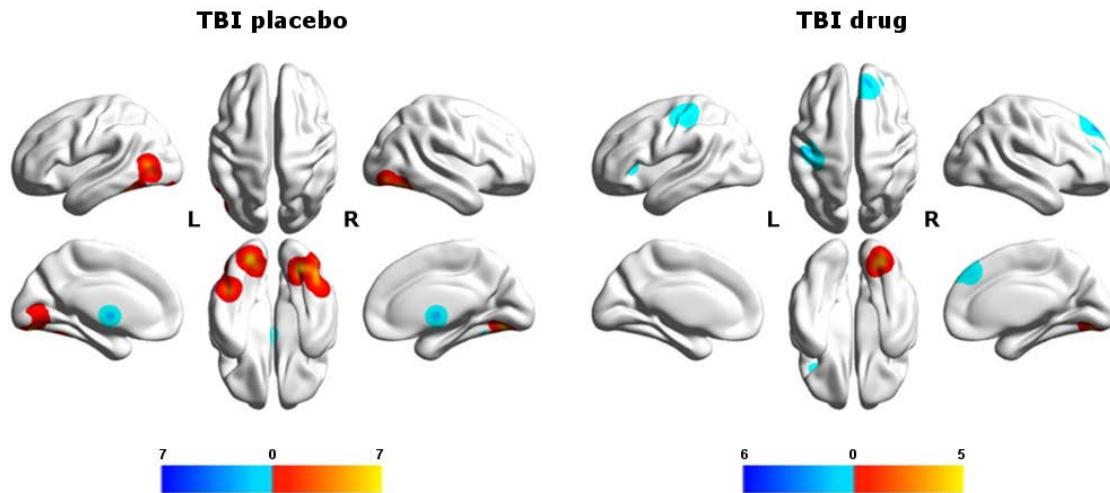
## Supplementary material

**Table S1.**

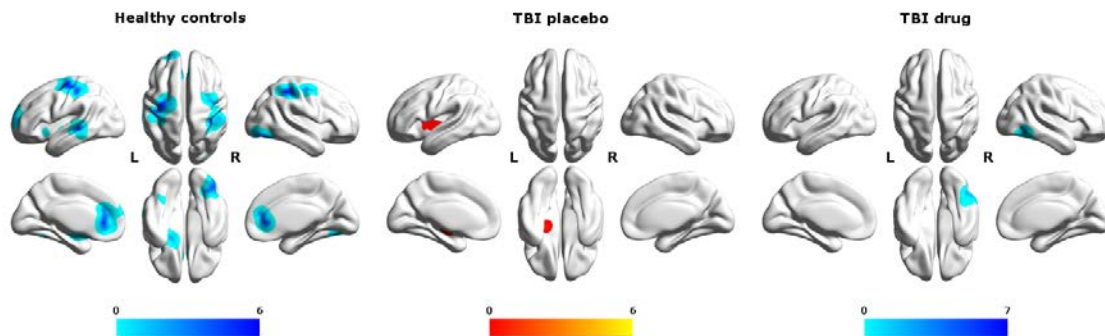
Patient	GCS	ISS	APACHE II	Days on ICU	Time since injury (months)	Mechanism of injury
1	5	25	21	18	36	Road traffic accident
2	7	26	16	5	25	Road traffic accident
3	10	9	19	7	32	Vehicle-pedestrian collision
4	8	9	13	8	27	Assault
5	12	17	14	1	17	Fall
6	5	25	11	24	14	Road traffic accident
7	7	41	10	3	32	Vehicle-pedestrian collision
8	14	18	12	-	9	Fall
9	8	9	13	24	7	Road traffic accident
10	6	34	22	5	11	Road traffic accident
11	7	13	13	3	25	Road traffic accident
12	-	-	-	-	41	Road traffic accident
13	9	20	-	6	7	Fall
14	8	18	10	10	8	Road traffic accident

M: male; F: female; GCS: Glasgow Coma Scale; ISS: Injury Severity Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II. ICU: Intensive Care Unit. GCS, ISS and days on ICU were not available for one patient. APACHE II was not available for two subjects.

**Table S1.** Lesion information of the participants



**Figure S1.** Brain activations and deactivations during the successful inhibition vs. unsuccessful inhibition contrast in the TBI patients. Results are displayed at  $P < 0.005$   $k > 50$ . Results are presented on inflated brains created using the BrainNet tool. The colour bars represent t-values.



**Figure S2.** Within-group positive and negative functional connectivity maps calculated from the seed found in the subtractive analysis (right IFG). Results are displayed at  $P < 0.05$  FWE. Results are presented on inflated brains created using the BrainNet tool. The colour bars represent t-values.